MUCO-EPIDERMOID TUMORS OF SALIVARY GLANDS

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FOR A NUMBER OF YEARS our attention has been directed to a group of salivary gland tumors differing structurally from commonly recognized tumors primary in these locations. Due to their infrequency and our inability to find adequate clinical and pathologic descriptions, these tumors for a considerable period constituted a several-sided problem as regards terminology, histogenesis and prognosis. Gradually, by correlating histologic structure with clinical course it became possible to dissociate two structural types, one indicating capability of localized growth, the other that of metastasis. A few of the tumors afforded unusual opportunity to establish their origin from salivary gland ducts and the group as a whole showed no structural interrelationship with other specific types of salivary gland tumors.

The term, "muco-epidermoid" salivary gland tumor, is one of our own choosing and, although not fully descriptive, it expresses two principal histologic features present in all of our cases. No pretense is made that these tumors are described herein for the first time. Beyond doubt both the old and more recent literature contain references to them but in a fashion insufficient for group analysis. It is certain that they deserve a more prominent place in the literature on salivary gland tumors than they now possess. We place their frequency at a little more than 5 per cent of all combined major and minor salivary gland tumors.

Lack of recognition and emphasis on these tumors is understandable. As a group they traverse an unusually broad range of histologic variation dependent upon the relative proportions of the different representative cell elements present, and tendencies to diffuse overgrowth by a single cell type. Gross appearance is not uniform. Sometimes the tumors are cystic and again they are solid. Some of them are encapsulated and others are not. The recurrent tumors may depart greatly from the structure seen in the primary. Unless analyses of salivary gland tumors encompass very large numbers of cases there is little probability that the full range of these muco-epidermoid tumors will be observed. It is likely that many of the tumors have been forced into classifications under such terms as "cystadenoma," "basalioma," "cylindroma," "squamous carcinoma" or "adenocarcinoma." Finally, there seems to be a certain reaction of frustration among pathologists which leads to relegating any odd salivary gland tumor to the broad, unfenced field of the so-called mixed tumor.

Lecène,[1] in a paper devoted to adenomas and cysts of the parotid salivary gland, showed an illustration, now difficult of interpretation, of a case bearing some resemblance to the group to be described. He regarded the tumor as different from mixed tumors. In this case Lecene stated that squamous

epithelium was absent; but the degree of alteration required before an epidermoid cell is referred to as squamous will vary among different observers. Fick,[2] in 1909, described and illustrated a probable case. He regarded this as an example of mixed tumor but the description rendered raises doubt as to this. Shortly after Lecène and Fick, in a discussion of cancer of the submaxillary salivary gland, Chevassu[3] reported a case that was probably of this muco-epidermoid type. It is interesting that he regarded the excretory ducts as the probable site of origin. Chevassu quoted an older case of Volkman[4] that seems equally probable. There is no doubt that a tumor described by Schilling[5] can be identified as a member of this group. His Figures 2, 3, and 4, taken from a single case, are entirely convincing. Krompecher[6] gives an account of a tumor of the lip that arouses speculation. In his opinion some tumors of mucosa and major salivary glands were of excretory duct origin. Ewing,[7] in his chapter on salivary gland tumors, lists several structural features that are common to muco-epidermoid tumors but presents no formal treatment of these as a separate histologic variety and simply includes them under the general heading of carcinoma. He regarded such tumors as ductal in origin. In Lang's[8] treatise on salivary gland tumors mention is made of a parotid tumor first classified as a round cell sarcoma but reclassified by Heineke as a papillary cyst carcinoma. Later this tumor was said by Schäfer to have contained mucous cells, and on this basis we may regard this as another probable case. Leroux and Leroux-Robert[9] in 102 major salivary gland tumors, found four with high cylindrical or clear mucous cells. Their photomicrographs show the presence of other cell types. These cases with little doubt correspond to the group to be discussed. These authors also speak of seven cases of "malpighian" type with squamous differentiation. It is difficult to ascertain if these cases represent mixed tumors with foci of squamous metaplasia or if they, too, are a type of muco-epidermoid tumor. Ahlbom,[10] in an extensive monograph devoted to salivary gland tumors, gives in collaboration with Reuterwall a thorough morphologic classification. Included in this are tumors listed as "papillary cystic." They are further designated as being benign, semimalignant and malignant. We would use the term, muco-epidermoid, certainly for some of these tumors, on the basis of Ahlbom's Figures 33 and 41.

Our review of literature related to salivary gland tumors has not included every article on this subject but it has been extensive with reference to important sources. Enough ground has been covered to give assurance that the type discussed in this paper has been dealt with very sparingly. These tumors are certainly not familiar objects. A great many of our sections have been shown to experienced pathologists who have expressed themselves as unacquainted with them as a specific group.

MATERIAL

The material for this analysis was obtained from the Memorial Hospital records of approximately 700 major and minor salivary gland tumors of all

types seen between 1928 and 1943. A total of 45 cases was found acceptable for inclusion. No case was selected in which it was not possible to demonstrate the presence of mucous cells, as shown by staining with Mayer's mucicarmine. In addition, every tumor had cells with epidermoid qualities—as will be defined in a later section. No case presented the structural characteristics of mixed tumors or other varieties of salivary gland tumors.

PATHOLOGY OF MUCO-EPIDERMOID TUMORS

Histogenesis.—In tracing the origin of muco-epidermoid salivary gland tumors it must be recalled that scattered mucous cells, though not uniformly present, can be found within the duct epithelium of a considerable number of major salivary glands. The same is true in minor salivary glands, but they are more difficult to demonstrate. Under normal conditions they are scarce and are more likely to occur within the lining of major excretory ducts. Their frequency decreases as the smaller duct radicals are approached and we have not observed them within intralobular ducts. Under pathologic conditions leading to chronic interstitial sialitis the number of mucous cells is apt to be greatly increased. During the course of this study we examined a large number of salivary glands that did not contain tumor but which had been removed on account of chronic interstitial sialitis. In such salivary glands mucous .cells were almost invariably found, sometimes in such striking numbers that they formed small, hyperplastic foci. In sections of whole glands the frequency and distribution of mucous cell aggregates was correlated closely with the pattern of the interstitial inflammation. In such cases we failed to discover mucous cells as far down in the duct system as the intralobular ducts.

Other cells of the salivary gland ducts include the rounded basal or malpighian cells, rounded or elliptical intermediate cells and the columnar cells. The latter are almost invariably nonciliated but on two occasions we were able to detect cilia, once in the parotid and once in the submaxillary salivary gland. The major excretory ducts usually have three to four basophilic cell layers but these gradually decrease as the salivary gland lobules are reached. The intermediate ducts have two layers, basal and columnar. These gradually become attenuated so that the intercalary ducts do not have two continuous cell rows. The columnar cells become more in evidence until they constitute the only discernible layer. As a single columnar cell-lining is established the cytoplasm assumes an eosinophilic quality. This occurs shortly before the duct branches enter the lobules and within these structures the eosinophilic properties of the duct epithelium are maintained.

All of the evidence in our material points to the salivary gland ducts as the anatomic site of origin of muco-epidermoid tumors. Two of the tumors in our series were very small, measuring only a few millimeters in diameter. They consisted in scarcely more than a collection of dilated ducts containing papillary or nearly solid tumor composed of appropriate cell types. There

was no evidence in these cases (or in others) of acinar participation. In more advanced tumors it was not uncommon to find closely adjacent or even outlying ducts in which there were hyperplastic foci. Such foci were made up of cell types identical with those constituting the main body of the tumor. The existence of such outlying foci (Fig. 1) may in part explain the fact that even the more favorable histologic forms of muco-epidermoid tumors are more apt to recur after surgery than are mixed tumors. In one tumor, recurrent when first seen at Memorial Hospital, a protruding nodule was seen distending Stenson's duct. The patient had complained of bloody saliva. After surgical excision, the tumor proved to be exclusively intraductal. Though much emphasis in this case is lost due to the fact that the tumor was recurrent, we have never seen a recurrence present in this particular fashion when the tumor was a member of a different histologic group. The occurrence of various cell types in the ducts of salivary glands has already been mentioned and when it is found that a series of salivary gland tumors is composed of multiple cell types and when these cell types are seen to correspond structurally to cells found in a certain anatomic location it is reasonable to implicate such a site as the source of origin for these tumors. This set of relationships holds true as regards salivary gland ducts and muco-epidermoid tumors. Having failed to secure evidence of the participation of eosinophilic cells in the tumors under consideration, emphasis is placed on the origin of such tumors in the larger and intermediate ducts.

Separation of the tumors into two histologic types: Early in this paper it was stated that muco-epidermoid tumors could be separated into two histologic varieties and for convenience these will be referred to as benign and malignant. These designations, however, require qualification. It might be preferable to speak of a "relatively favorable" and a "highly unfavorable" group. The term "benign" is scarcely ever applicable in an absolute sense and as used here does not necessarily imply innocent behavior. It does mean that thus far we have not observed metastasis from such tumors. The term "malignant," when employed here, indicates a histologic structure which has been found associated with the ability to produce regional node and distant metastases. It, of course, does not mean that such an event is inevitable.

The authors freely admit that they suffered a long period of uncertainty as to the status of some of these tumors. Some initial impressions proved unreliable. These were corrected from time to time by checking histologic findings with clinical course. Finally, we began to catalogue cases in which metastases had been proven. Structural features in these tumors were studied and as these cases accumulated a practical working basis was formed for defining a known malignant group. Simultaneously, other cases were catalogued whose clinical course did not include the appearance of metastases. There remained a small number of cases of troublesome sort that were regarded with suspicion on account of a certain structural feature. This consisted of nearly diffuse epidermoid or squamous overgrowth of a quality

to be commented on in another section. Enough familiarity with these tumors has now been gained to be reasonably certain that they do not belong in a metastasizing group. There is a residual impression, none the less, that they are quite prone to recurrence and that some of these recurrences are definitely malignant.

In arranging material for the present study all of the slides were assembled in numerical order. Each was then estimated to determine whether or not it showed a malignant tumor. This was done without recourse to case histories. This analysis proved the validity of previously established histologic criteria of malignant behavior since on review of clinical records no case classified as "benign" furnished any evidence of metastasis. On the other hand, many of the cases classed as malignant had developed metastases. This dissociation of cases seemed necessary in order that the histologic and clinical traits of the benign and malignant tumors could be separately discussed.

Cellular Interrelationships.—Since, in the foregoing, a number of separate cell types have been mentioned as being present in muco-epidermoid tumors it can well be imagined that structural patterns will be numerous and varied. Before describing the microscopic patterns that characterize muco-epidermoid tumors it is desirable to discuss in some detail certain fundamental cellular proliferations and transformations that take place in these tumors. Whereas, they are seen with greater clearness in benign tumors, they are discernible in a considerable portion of malignant tumors. In addition to the study of the tumors themselves, observations of duct hyperplasias in glands free from tumor yield certain impressions concerning cell behavior.

The basal cells appear to be pluripotent and capable of differentiation directly into tall columnar epithelium or directly into rounded mucous cells. It also seems that the columnar cell may be a relatively fixed type or represent an intervening form prior to the assumption of mucus forming properties. In foci of orderly duct hyperplasia where there are many cell layers both columnar and mucous cell differentiation tend to occur at the luminal margin rather than at the basement membrane (Figs. 5 and 6). Thus, in such focal areas the middle zones are apt to be composed solely of intermediate or basal cells. Here and there, however, one may find some cells that have rather pale cytoplasm, are rounded and slightly or considerably larger than basal cells. The quantity of cytoplasm in these cells is increased and is pale in varying degree. If such sections are stained with Mayer's mucicarmine this pale quality of the cytoplasm marks the presence of mucus. The intensity with which the cells take the stain is variable and since mucus can be shown in round cells only slightly larger than basal cells it is evident that mucous change can occur without intermediate formation of large columnar cells. By similar means large columnar cells can be seen to acquire increasingly intense mucicarminophilic properties finally forming fully developed goblet cells.

The formation of columnar cells in these tumors may be referred to as the result of proliferation and differentiation, the latter term being chosen

FIG. 1

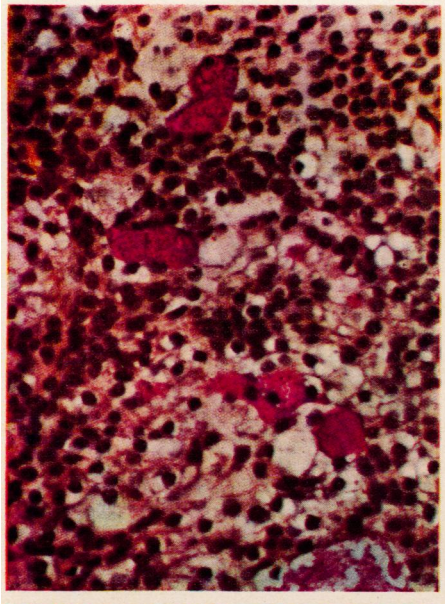
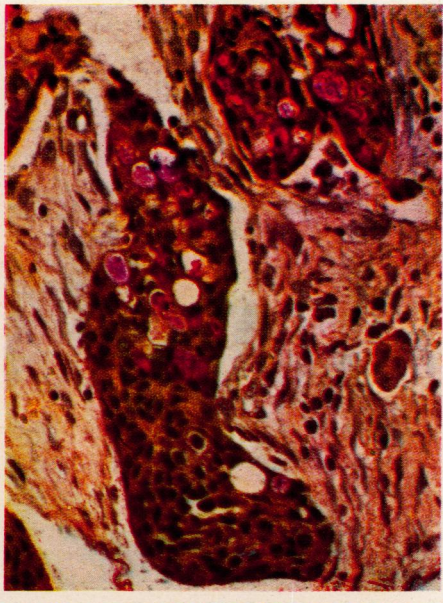


FIG. 2



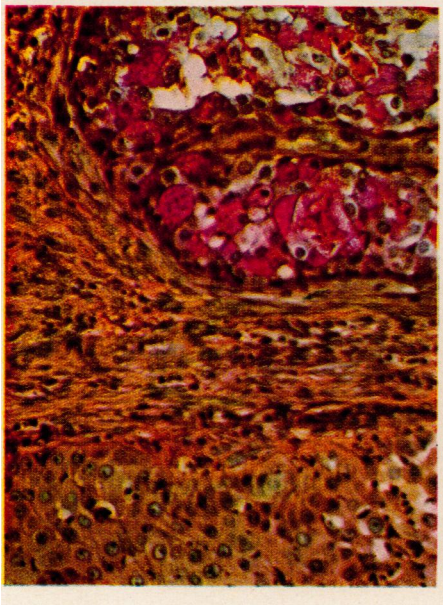


FIG. 3

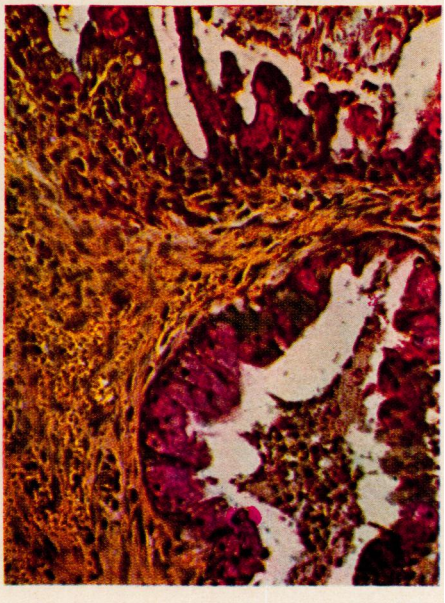


FIG. 4

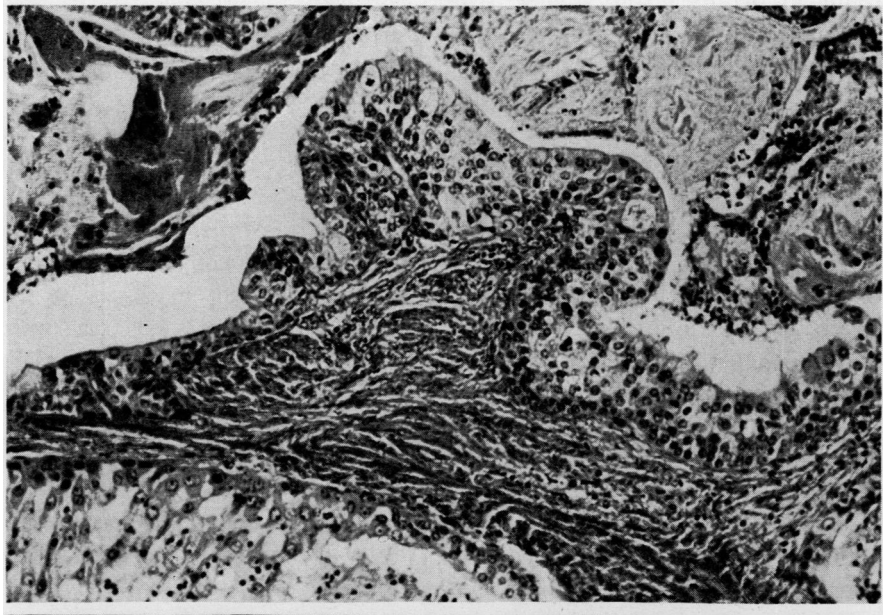
FIG. 1.—Periphery of a benign parotid tumor. Stratification and papillary hyperplasia of pink-staining mucous cells. (Iron hematoxylin, metanil yellow and mucicarmine.)

FIG. 2.—Same tumor as Figure 1. Diffuse epidermoid and squamous area adjacent to one rich in mucous cells.

FIG. 3.—Epidermoid and mucous cells in a malignant tumor of the parotid salivary gland. Regional nodes contained metastases.

FIG. 4.—Subcutaneous axillary metastasis from a primary tonsillar tumor. Large mucous cells, basal and intermediate cells. Note hydropic cells that do not take mucicarmine stain.

FIG. 5



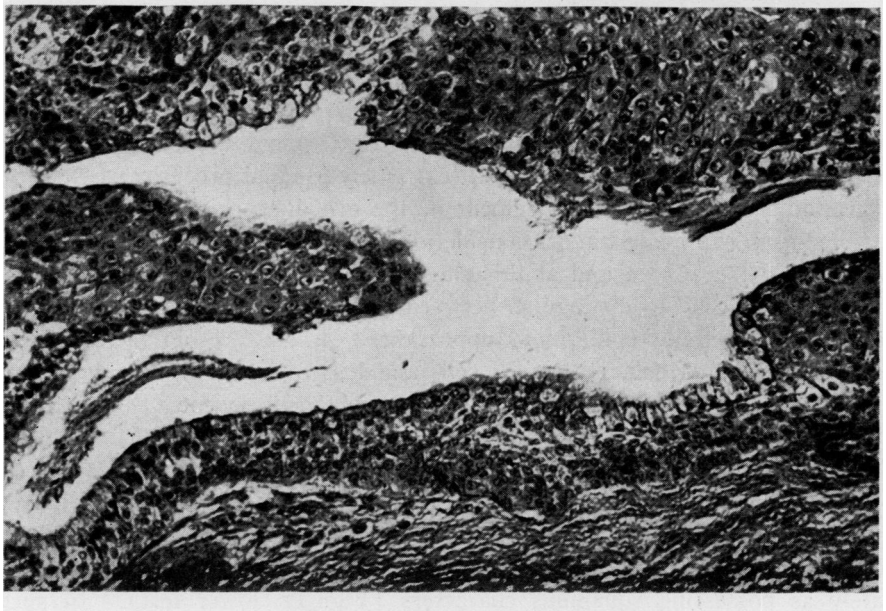


FIG. 6

FIG. 5.—Benign parotid tumor. Duct distended with mucus and cell débris. Varying degrees of stratification. Transitions from basal to intermediate and mucous cells. Two cells in mitosis.

FIG. 6.—Benign parotid tumor. Multiplicity of cell types discernible in limited area.

since columnar cells are distinctly normal constituents of salivary gland ducts. In neither the benign nor the malignant tumors are columnar cells a prominent feature quantitatively. In no case were they a dominant element and in an over-all sense they were few. Perhaps this cell type, when formed, has relatively limited powers of proliferation or perhaps the basal cells tend to lose their ability to differentiate into this form.

Since mucous cells are very sparse in normal salivary gland ducts their presence in muco-epidermoid tumors may be referred largely to a process of metaplasia, that is, abnormal differentiation. Initially, it is presumed that the basal cells furnish the chief source of mucous cells. There is much evidence, however, that mucous cells, once formed, have considerable powers of proliferation. Very large as well as limited areas in some of the tumors were made up chiefly of this cell type. Mitoses in such areas were very rare and it is not easy to point out a single cell in mitosis and declare with assurance that it is or is not a mucous cell. In the upper, central portion of Figure 5 are two cells, probably of mucous type, in mitosis. In mucicarmine preparations occasional cells in mitosis have been observed to exhibit distinctly pink cytoplasm. Quantitatively, mucous cells were much more conspicuous in the benign than in the malignant tumors. In those dominantly mucous cell tumors epidermoid cells were by no means as plentiful as the basal or intermediate type.

Epidermoid metaplasia is one of the outstanding cytologic characteristics of both classes of muco-epidermoid tumors. Whereas, the basal cells are by all odds the principal type involved in this transformation there is satisfactory evidence from a good many tumors that both mucous cells and columnar cells may also undergo similar changes. Epidermoid metaplasia of basal cells when all stages are studied is an extremely gradual process and the first alteration involves slight enlargement of the cell due principally to increase in cytoplasm. In many tumors considerable areas of this sort of intermediate differentiation are seen and at this stage we have often employed the term "intermediate cell" to distinguish between the basal cell and one which possesses more definite epidermoid appearance. Further progressive change involves continued enlargement of cells and loss of uniform, round or oval cytoplasmic border. Certain cells assume a polygonal outline (Fig. 6, upper right), the nucleus becomes a little larger and more vesicular. At this stage the epidermoid cells are about twice the size of basal cells. If the process of metaplasia proceeds further, the cytoplasm becomes increasingly abundant and more opaque. With this degree of change the epidermoid cells are three to four times the parent cell size and can actually be described more accurately as possessing squamous characters (Fig. 12, lower left). In such cell areas as this it is not uncommon at high magnification to detect canalicular channels between the cytoplasmic limits of adjoining cells but when such structures are seen they are very seldom accompanied by the formation of intercellular bridges. Fully developed squamous differentiation with development of keratohyalin granules, intercellular bridges, and pearl formation

are seen in the exceptional case with great clearness (Fig. 8). When epidermoid and squamous metaplasia stem from columnar or mucous cells the process is not sufficiently different from that already described to justify repetition. Cells that have differentiated along epidermoid or squamous lines seem to develop greater powers of proliferation than those which have become columnar or mucous. Diffuse epidermoid overgrowth occurs in both the benign and malignant tumors sometimes to such an extent that multiple sections and mucicarmine staining are necessary before they can be classed in the group under discussion.

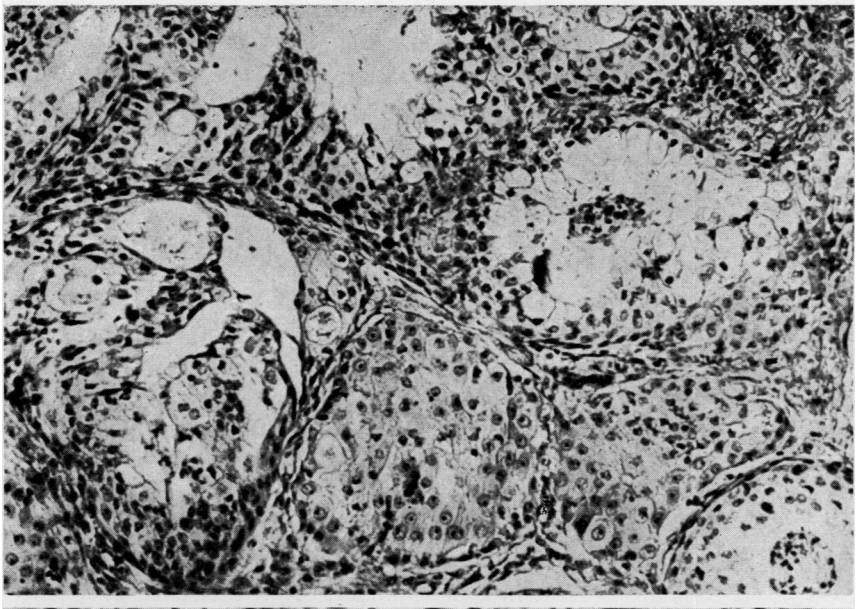
HISTOLOGY OF THE BENIGN TUMORS

In the 26 benign tumors the predominant cells were epidermoid in 14, mucous in nine and intermediate or basal in the remainder. In the majority at least three cell types were represented. Tumors that included appreciable numbers of every cell type described were rather exceptional even when many blocks of tissue were sectioned. The presence of multiple cell types in large numbers was more distinctive of benign than malignant tumors.

The most highly characteristic tumors (Fig. 6) are necessarily those which contain reasonably large numbers of all of the various cell types described. Seldom does one see an area of even a few millimeters in which these various cells are present in equal number. In a restricted area pattern depends a good deal on which type of cell is predominant. For example, if the basal or intermediate cells predominate, a uniform mosaic results and the constituent cells tend to be arranged in quite small to quite large sheet-like groups which may make up only a small part of a low power field or may encompass an area many times as large. The peripheral margins of such cell masses are usually quite clearly delineated somewhat as is seen in basal cell epithelioma or sweat gland adenoma. In such areas solid growth is the rule and if there are openings or pseudoglandular spaces, other cell types are almost invariably present.

In areas particularly rich in mucous cells the above-described sheet-like growth quality is unexpected (Figs. 5 and 7). Instead there are quite small or even greatly dilated duct-like structures which are lined sometimes by several, oftentimes by a single cell layer. Here and there will be knob-like epithelial excrescences whose cell members, though chiefly mucous in type, are seldom exclusively so. Some areas of mucous cell preponderance assume distinctly papillary qualities but these papillae only infrequently possess a central core of vascularized fibrous tissue. In other words, true papillary cystadenomatous structure is uncommon. When such structure is present, nonmucoid columnar cells are apt to be seen in their greatest frequency. In those portions of tumor which are duct-like or cystic the greatest multiplicity of cell types is apt to be encountered. Such areas, whether they are of microscopic or macroscopic size, are commonly found partly or entirely filled with mucoid secretion (Fig. 5) which stains brilliantly red with Mayer's mucicarmine (Fig. 1). Such "mucus pools" were found in about one-half

FIG. 7



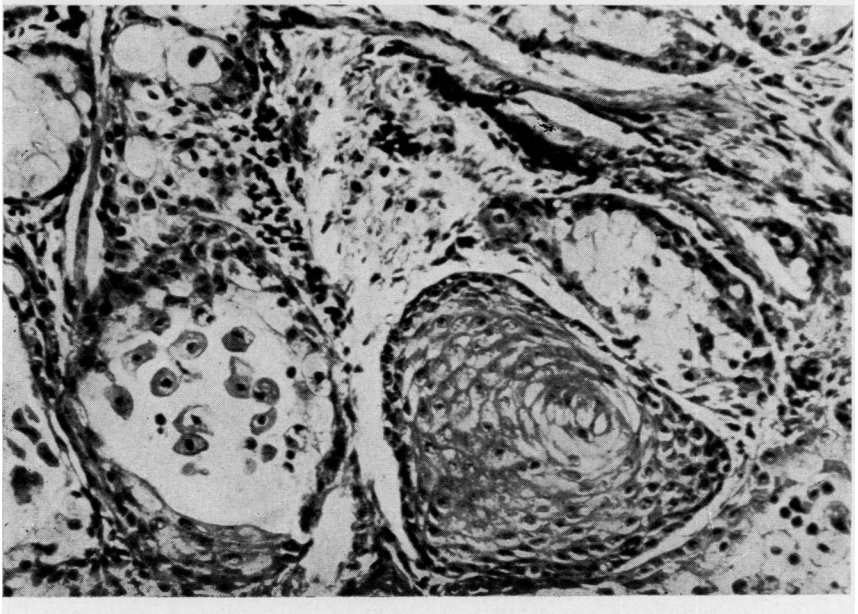


FIG. 8

FIG. 7.—Structure commonly seen in benign tumors. Mucous and epidermoid cells in abundance, the latter assuming some squamous qualities. Small numbers of basal and intermediate cells, their distinction not easy. Primary parotid tumor.

FIG. 8.—Benign tumor of tongue. Squamous pearl in a predominantly mucous cell area.

of the benign tumors. As a result of overproduction of mucus, considerable dilatation commonly ensues and the result of this is the erosion of lining epithelium, disruption of basement membrane, and leakage into adjacent tissue (Fig. 10). If this takes place in a near solid portion of tumor, small or larger areas of necrosis result. If there is leakage into an area where there is considerable interstitial tissue, a marked secondary inflammatory process is likely to ensue. Hence, in tissue adjacent to ruptured "mucus pools," it is not uncommon to see a well-developed foreign body reaction with formation of multinucleated giant cells.

In studying foci made up chiefly of epidermoid cells (Figs. 6 and 9), it is unusual to find complete dissociation from basal or intermediate cells but if the epidermoid differentiation has developed further so as to assume squamous qualities, there is apt to be extremely diffuse unicellular overgrowth. In such diffuse areas there is a certain monotonous regularity of structure difficult to describe but of a distinctly different type than that seen in squamous carcinoma in the usual sense. There is greater similarity in cell size and shape, staining qualities are quite uniform, and mitoses are few. It is in such areas as these that one is apt to regard the tumor as malignant and considerable familiarity with its structure is needed before one feels confident of expected clinical behavior (Fig. 2, lower half). In the benign tumors, the squamous areas referred to above tend to grow in relatively large sheets and plugs but in some tumors these become quite small and in the process of fixing and dehydration, shrinkage is apt to cause contraction so that the epidermoid or squamous plugs give the false impression of lying within lymphatics. Whereas this false impression of lymphatic invasion is usually easily settled by careful high-power study adjacent connective tissue cells are sometimes capable of simulating flattened endothelium.

Before concluding this description of microscopic features an additional cytologic alteration should be described. In about a third of the benign tumors, certain areas were composed of cells that appeared hydropic and swollen. They had extraordinarily clear cytoplasm (Fig. 11). When this change was highly developed and the cells in alveolar or pseudoglandular grouping, there was effective mimicry of clear cell renal adenocarcinoma. Since the collection of material for this paper we have seen a biopsy of a submaxillary tumor in which this structure was so prominent that it was necessary to have assurance that there was no clinical evidence of renal neoplasm before making the diagnosis of muco-epidermoid salivary gland tumor. Sections of the excised tumor eliminated any doubt of its muco-epidermoid nature. When these hydropic changes are present, they might lead one to suspect that such areas had undergone mucous transformation. In none of our cases, however, did such cells stain with Mayer's mucicarmine.

To sum up, in any benign tumor there may be a very wide range of structural variation dependent upon the frequency of individual cell types and the growth pattern that such cells seem to follow. This is further modified by the presence of secondary phenomena such as overproduction of

mucus, distention of canalicular components, secondary interstitial inflammation, and spontaneous necrosis.

HISTOLOGY OF THE MALIGNANT TUMORS

An over-all analysis of the cytology seen in the malignant tumors showed rather definite trends. For example, in none of this group of 19 tumors did mucous cells predominate, and in only eight of these were mucous cells the second most frequent element. Epidermoid cells were dominant in 14 of the 19 tumors (Figs. 3, 12 and 13). It is understood that the term epidermoid, as used here, includes cells which resemble those seen in basal cell carcinoma and also those cells which have been described as resembling squamous cells without intercellular bridges and keratohyaline granules. Another frequent cellular component of the malignant tumors was the intermediate cell which, it must be admitted, is difficult to distinguish verbally from the basal cells other than by saying that they are slightly larger, have somewhat more vesicular nuclei and more abundant cytoplasm (Fig. 17). Columnar cells, as in the benign tumors, were infrequent in the malignant tumors. When present they were not numerous. In one tumor it was possible to identify a few ciliated columnar cells. True squamous cells having intercellular bridges and epithelial pearls were found in five cases. There were four other cases in which intercellular bridges alone were present.

When the malignant tumors and benign tumors are studied as individual groups wide structural divergences are apparent. There is, however, an undertone of similarity varying in degree from case to case. Now and then a case is met in which a remarkable series of cellular alterations has occurred so that the entire gamut of changes characteristic of both the benign and malignant types is seen. If, however, one studies a highly mucoid and epidermoid tumor of the benign group and then one of the very diffusely overgrown rather anaplastic malignant tumors, he would probably not be very much impressed by the interrelationship of these two types of muco-epidermoid salivary gland tumors. Further means of integrating the benign and malignant tumors as members of the same fundamental group are secured by studying structural changes in succeeding recurrences. In several cases the initial structural characters were those of a benign tumor made up of mucous and epidermoid or squamous cells in orderly arrangement. In recurrences, diffuse epidermoid overgrowth has taken place together with the development of atypical cell qualities such as characterize the malignant tumors. The scope of changes observed in the transformation of a benign into a malignant muco-epidermoid tumor traverses no wider range of structural alteration than may be met in the case of a mixed tumor of salivary gland which has become malignant. It must be emphasized that the large majority of malignant muco-epidermoid tumors do not contain residual microscopically benign elements. We were at first skeptical about including some tumors in the malignant group but were finally convinced of their suitability after having studied that material which showed transitional

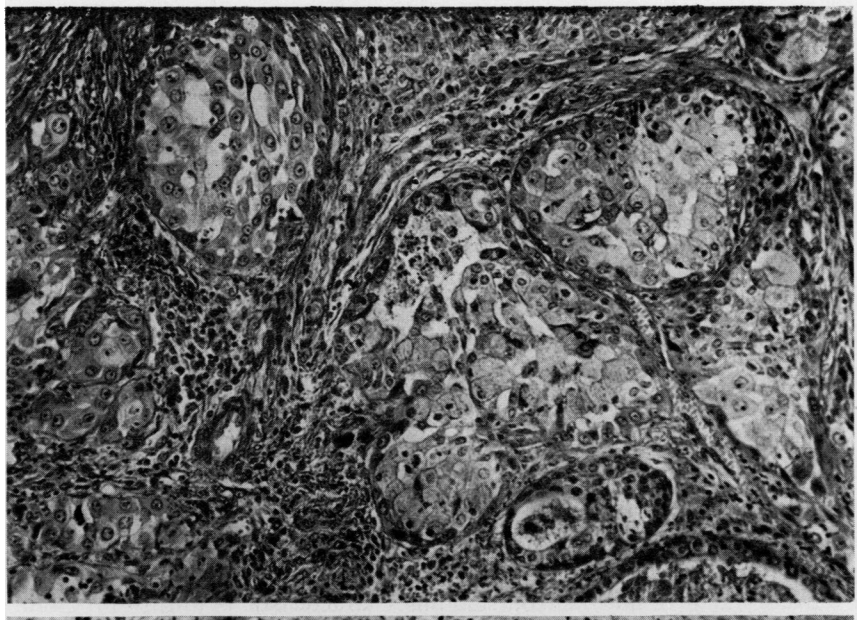
phases. Due to almost complete overgrowth by epidermoid or squamous cells many of the tumors are apt to be regarded as unicellular cancers of either epidermoid or squamous type. In such cases, however, careful study will reveal small nests, minute groups or even single cells of different sort. Some isolated cells which appear rather pale but finely granular can be proved by mucicarmine staining to contain mucus. It is repeated that no tumor has been included in this series in which a mucicarmine stain was negative. We believe in all probability that a certain number of rather anaplastic and diffuse cancers of salivary glands are fundamentally muco-epidermoid in type but have become so overgrown that the mucous element is no longer discernible. This is perhaps especially true in that group of salivary gland tumors referred to by most observers as squamous or epidermoid carcinoma. In our own material we have quite a number of such tumors but when they have proceeded to this degree of homogeneity, we have excluded them from consideration here.

The histologic qualities which separate the malignant from the benign tumors are for the most part easily recognized. These traits are not substantially different from those ordinarily present in epidermoid and squamous carcinoma and as such do not require further comment (Figs. 13 and 16). The remainder of the malignant tumors may exhibit these qualities in slight or moderate degree but their outstanding characteristic is diffuse proliferation of rather small, moderately hyperchromatic, rounded and oval cells in sheet-like arrangement with tendency to palisading of the outer layer of cells which surround the proliferating sheets and pegs of tumor (Fig. 15). A general structural impression is that of the gross pattern of a basal cell epithelioma with something added. There is appreciable resemblance to some of the highly cellular transitional cell carcinomas of other locations. Rather than continuing in the effort toward verbal descriptions, it is preferable to refer the reader to Figures 12, 13, 15–18.

Other structural differences become evident when comparing the benign and malignant tumors. The latter show little tendency to formation of microcysts. Tubular and papillary features are far less frequent. Over-secretion of mucus with the production of mucus pools practically never occurs. For obvious reasons secondary inflammatory changes, referable to the leakage of mucoid material, are highly exceptional. Sometimes present in the malignant tumors are pseudoglandular structures. These are by no means common. In one case having such structures they were partly composed of mucous cells. In this case some portions were hard to separate on structural grounds from mucous gland adenocarcinoma.

Analysis of the histologic structure of the metastatic tumors revealed some points of interest. The variable structure of the primary tumors was sharply reflected in such lesions. By way of illustration, on more than one occasion the metastatic lesions were distinctly more epidermoid or squamous than the primary. The reverse of this was also seen. Moreover, in a single metastatic nodule considerable variation was observed (Figs. 16 and 17).

FIG. 9



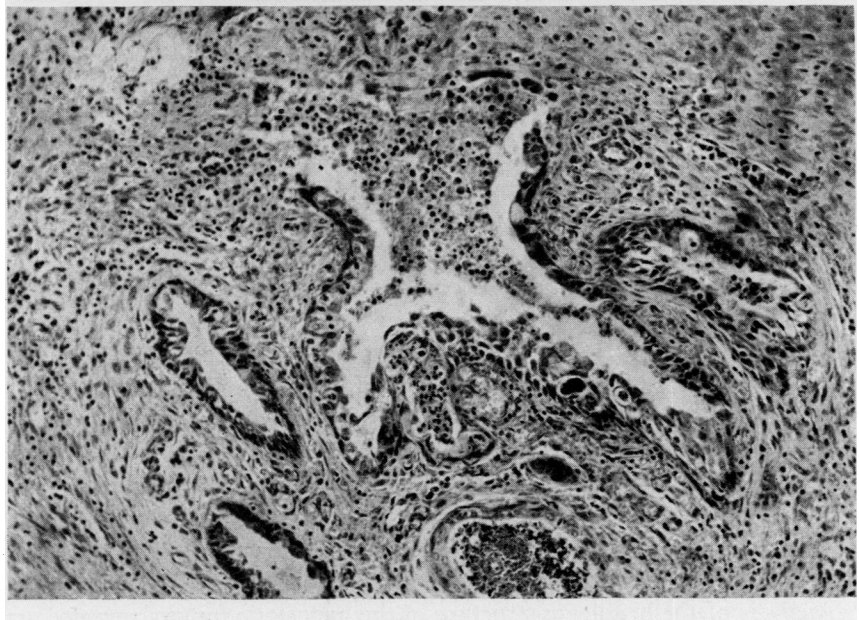
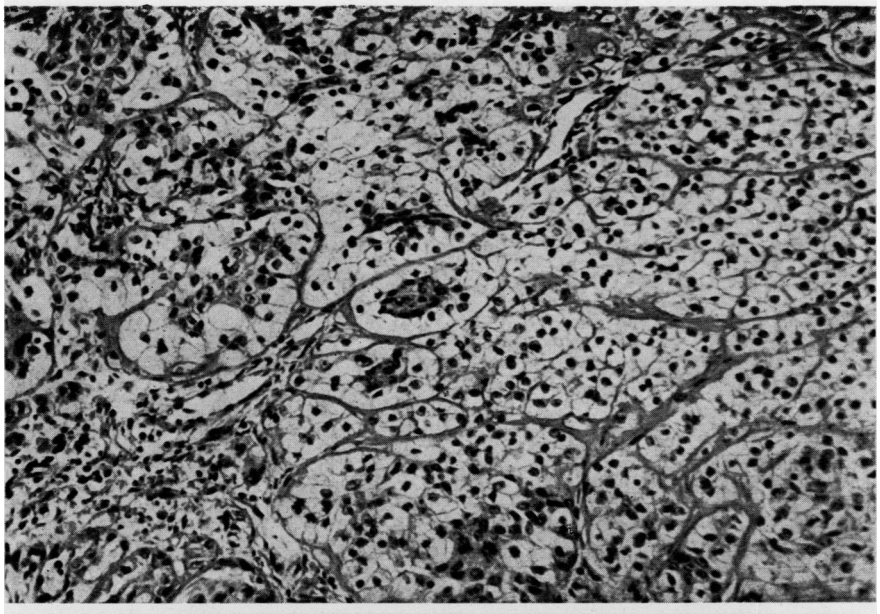


FIG. 10

FIG. 9.—Benign tumor of parotid. Cellular make-up largely epidermoid but showing intermingled mucous and basal cells.

FIG. 10.—Erosion of epithelium, leakage and interstitial inflammation.

FIG. 11



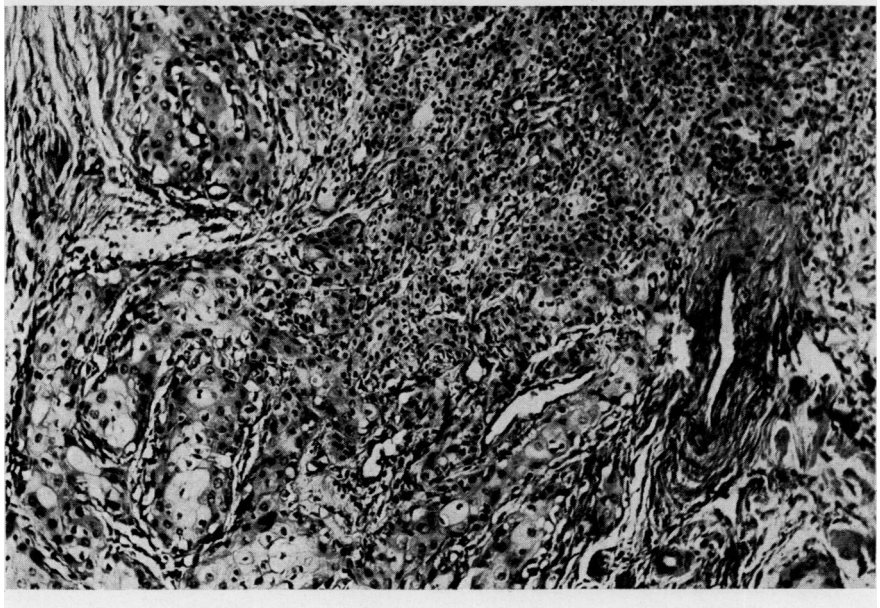
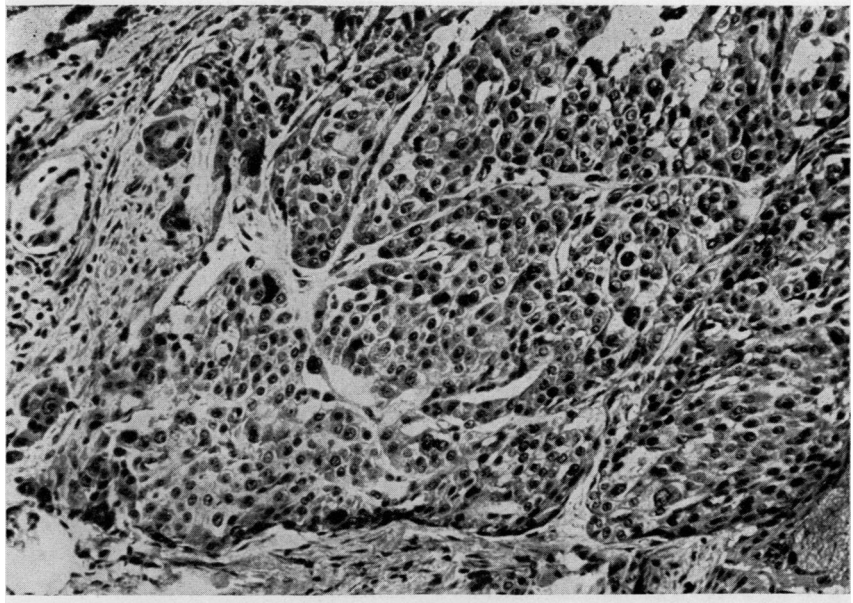


FIG. 12

FIG. 11.—Structure resembling clear cell renal adenocarcinoma. Regarded here as benign.

FIG. 12.—Transition of basal to epidermoid and squamous cells in a malignant parotid tumor with multiple cervical node metastases.

FIG. 13



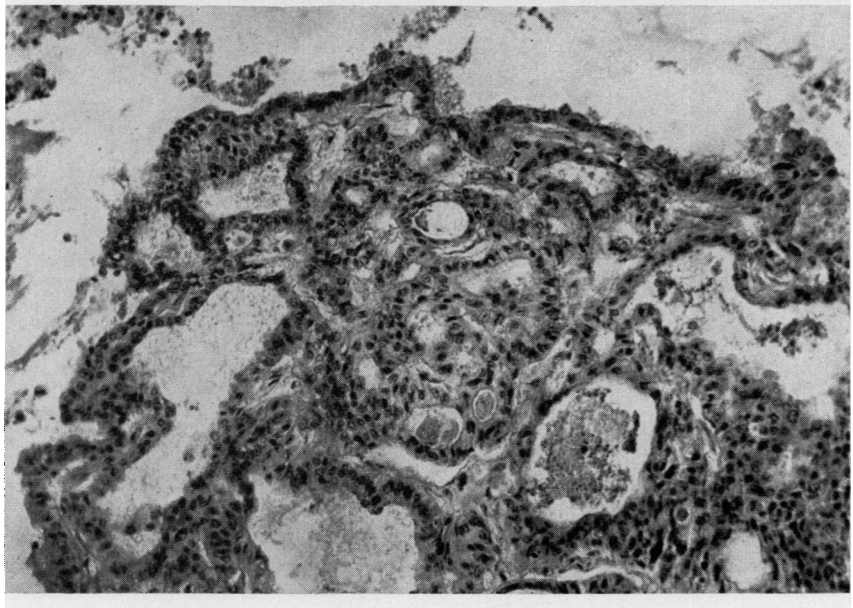
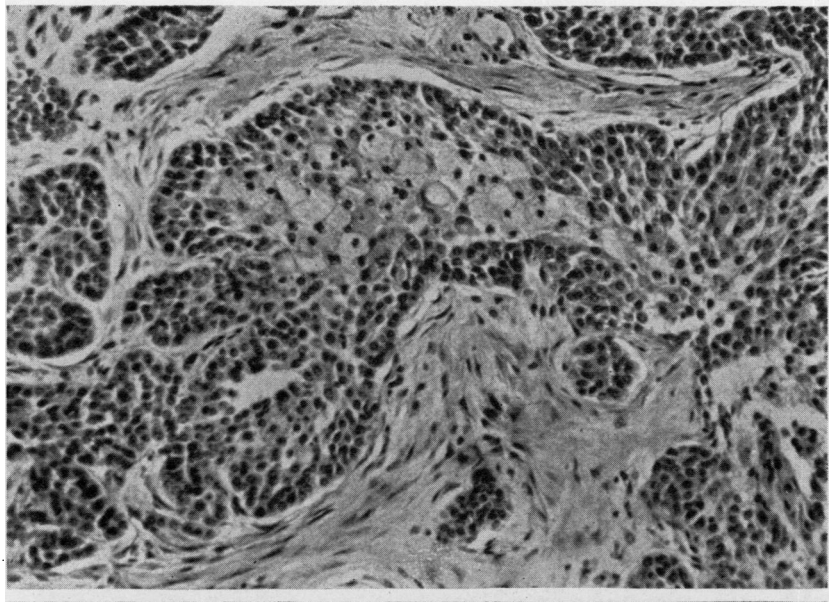


FIG. 14

FIG. 13.—Portion of an alveolar ridge tumor. Present for 25 years. Malignant transformation with structure of epidermoid carcinoma. (See also Figure 14.)

FIG. 14.—Another area of tumor shown in Figure 13. Growing here as papillary cystadenoma, benign.

FIG. 15



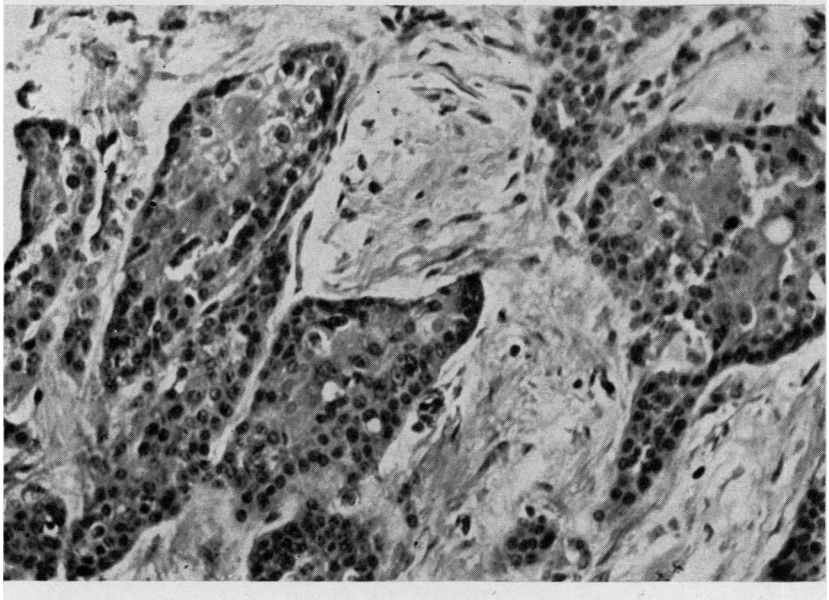
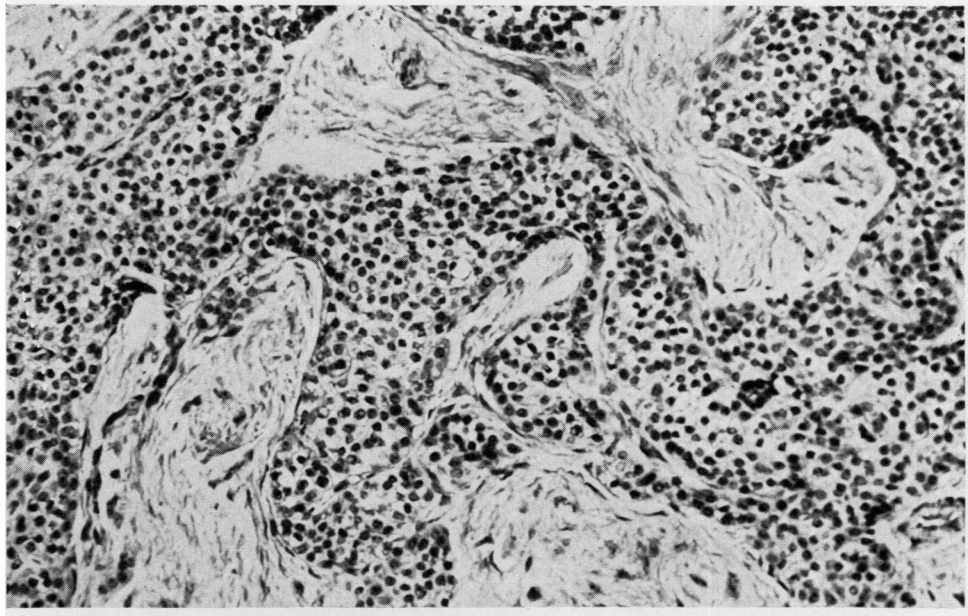


FIG. 16

FIG. 15.—Malignant muco-epidermoid tumor of tongue. Basal and intermediate cells merging with mucous cells; the latter stained intensely with mucicarmine. (See also Figures 16 and 17)

FIG. 16.—Metastasis to subcutaneous tissue of scalp from tumor in Figure 15. Cells exhibit squamous and epidermoid characters.

FIG. 17



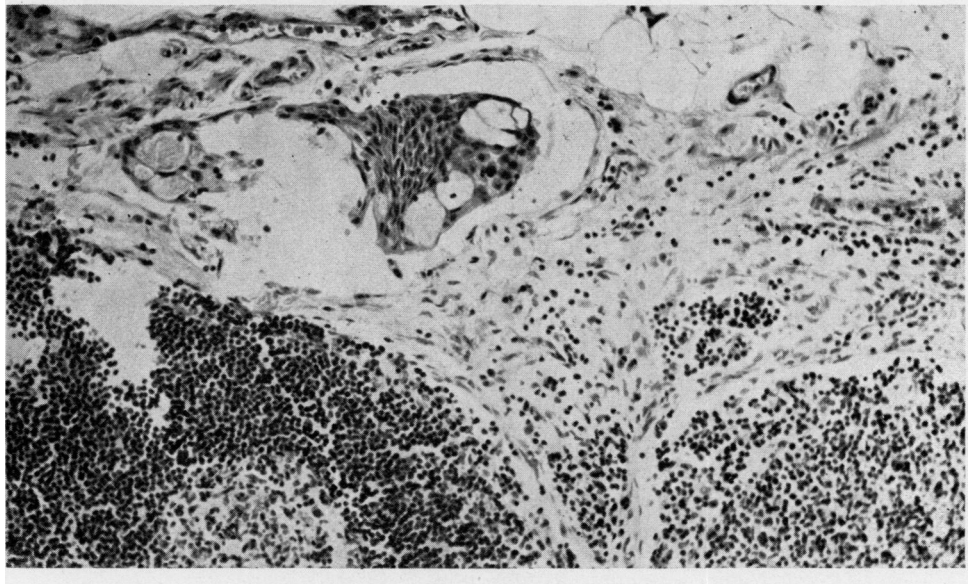


FIG. 18

FIG. 17.—Another area of the metastatic nodule seen in Figure 16. Intermediate cells.

FIG. 18.—Embolus in afferent lymphatic from malignant parotid salivary gland tumor. Several mucous cells are included.

It was possible to demonstrate mucous cells in large numbers in the metastases of four tumors and in moderate number in a fifth. In this connection Figure 4 may be consulted.

GROSS PATHOLOGY OF THE BENIGN TUMORS

Observations here are based on findings in 14 primary and nine recurrent tumors. As a rule they did not reach large dimensions. The largest tumors measured 4 cm. in greatest diameter. One was a centimeter in diameter and the smallest measured only 4 mm. The majority ranged from 2 to 3 cm. in greatest dimension. Regardless of location they tended to be ovoid in shape. Usually they were fairly well circumscribed but a well-developed capsule was present in only four of the 26 benign tumors. Poor encapsulation was the general rule and four were unencapsulated. The foregoing gross qualities were evident regardless of whether the tumors were primary or recurrent. Of some importance was the finding that some of those tumors which appeared rather well encapsulated in the gross did not show such sharp delimitation in microscopic sections. The lack of encapsulation in an occasional case was impressive and was further complicated by abundant mucoid secretion with leakage into adjacent tissue spaces. Extensive, locally infiltrative growth followed in a manner somewhat reminiscent of the local spread of some colloid carcinomas.

Before sectioning, most of the benign tumors were moderately firm but in most instances lacked extreme induration. The degree of firmness, however, differed widely among those tumors that were variously cystic or solid. On cut section the majority were at least partially cystic, the cystic spaces usually being multiple and from two to three millimeters in diameter. There were extreme examples where very large cystic cavities, one or more in number, comprised the bulk of the tumor. Some of the tumors were solid in one or more areas, unicystic or multicystic in others. Still others showed no gross cyst formation. The cystic spaces invariably contained nearly clear, opalescent or blood-stained mucoid material usually moderately viscid but sometimes thin. In tumors that were principally solid, lobulation was seldom seen and the cut surfaces were usually grayish-white or grayish-pink. In about half of the tumors there was discoloration due to secondary hemorrhage and/or necrosis.

GROSS PATHOLOGY OF THE MALIGNANT TUMORS

Of the 19 malignant tumors there were nine in which no surgical excisions were done and, hence, only ten gross specimens were available for study. Of these, four were primary and six recurrent. Here, as in the benign tumors, large bulk was not a pronounced characteristic since the largest tumor was 5 cm. in diameter and the majority were 2 to 3 cm. in greatest dimension. Lack of encapsulation was a distinct feature. Ordinarily they were obviously infiltrative and only a few were circumscribed. When compared with the benign tumors there was much less tendency towards cyst formation. Two tumors were grossly cystic but this was obviously the result of necrosis.

None of the ten tumors showed grossly visible mucus aggregates. They were distinctly firm, cellular, opaque, gray-white and homogeneous. Hemorrhage and necrosis were fairly common.

CLINICAL ASPECTS

Sex was not a factor in muco-epidermoid tumors since both the benign and malignant tumors were approximately equally divided between males and females.

The factor of age is represented in Table I from two points of view, namely, the age of the patients at the onset of the first symptom and the age when first seen at Memorial Hospital. (Ages are recorded in years according to the nearest birthday.)

TABLE I

Benign Tumors			Malignant Tumors		
Case No.	Age at Onset of First Symptom	Age When First Seen at Memorial Hospital	Case No.	Age at Onset of First Symptom	Age When First Seen at Memorial Hospital
2	16	17	1	34	36
3	38	39	4	69	70
5	42	43	8	64	66
6	21	22	9	25	50
7	39	40	11	74	75
10	26	28	14	36	44
12	56	59	16	11	12
13	54	57	22	35	36
15	54	59	23	49	54
17	7	8	30	?	18
18	56	56	32	63	63
19	43	44	33	59	60
20	31	36	34	62	64
21	38	40	36	52	54
24	23	26	38	56	57
25	41	43	39	43	44
26	24	25	40	48	49
27	20	21	41	13½	16
28	48	49	42	55	61
29	34	39			
31	22	28			
35	23	48			
37	34	35			
43	59	60			
44	41	42			
45	42	45			

From Table I it is evident that there is a general trend for the benign tumors to occur in a younger age group. Thus, when based on the age of patients at the onset of the first symptom, 42 per cent of the benign tumors occurred in patients over 40 years of age, whereas, 65 per cent of malignant tumors were in patients older than this. Similarly, only 25 per cent of benign tumors occurred in people over 50 years of age, whereas, approximately 50 per cent of malignant tumors were in patients 50 or more years old. The youngest patient was seven and one-half years old at the onset of the first symptom. This tumor was benign and arose in the parotid salivary gland. The youngest patient with a malignant tumor was 11 years old, and this tumor was also of parotid origin. No case among the benign tumors was

as much as 60 years of age when symptoms began, whereas, about one-fourth of the malignant tumors first gave symptoms after the patient was at least 60 years of age.

LOCATION

The distribution of both benign and malignant muco-epidermoid tumors is shown in Table II:

TABLE II

LOCATION OF FORTY-FIVE MUCO-EPIDERMOID SALIVARY GLAND TUMORS

	Benign	Malignant
Parotid salivary gland	20	7
Submaxillary salivary gland	1	2
Sublingual salivary gland	0	1
Minor salivary glands (including mucous glands of nasal cavity):		
a. Mucosa of cheek	1	
b. Mucosa of hard palate	1	
c. Mucosa of faucial tonsil	1	1
d. Mucosa of nasal cavity	1	3
e. Mucosa of tongue	1	2
f. Mucosa of alveolar ridge		2
g. Mucosa of nasopharynx		1

Table II shows that the parotid salivary glands were distinctly the most common sites of both the benign and malignant muco-epidermoid tumors. The bulk of these tumors was benign. Other major salivary glands were only exceptionally involved. Nearly one-third of the tumors arose from minor salivary glands in a variety of locations. It is noteworthy that most of these tumors were malignant. Thus, the general anatomic distribution of muco-epidermoid tumors is largely similar to that of other classes of salivary gland tumors.

SYMPTOMATOLOGY

Benign Tumors: Outstanding as an initial symptom in the benign tumors was painless swelling. This was true in 22 (85 per cent) of the 26 benign lesions. The first symptom in one case in which the tumor arose in the hard palate was pain after eating. In another case continuous throbbing pain developed in the region of the parotid salivary gland. Two of the benign tumors were discovered accidentally during the course of routine physical examination. Local pain developed at some subsequent date in about one-fourth of the benign tumors. A later development in one case was the appearance of bloody saliva. In none of the benign lesions was there any presenting symptom related to facial nerve involvement. In almost all of the benign tumors the rate of growth under observation, or as related by the patient, was described as quite slow or apparently stationary. In none of these cases was impressively rapid growth recorded.

Fifteen of the 26 patients with benign tumors had not been treated prior to admission at Memorial Hospital and the duration of symptoms in these cases was accurately recorded. There was wide fluctuation. Nine had had one or more symptoms for a year, or more. In six of these nine, more than

two years had elapsed since symptoms began and in two patients the tumors had been known to be present for at least five years.

Malignant Tumors: The symptom complex observed in the 19 patients with malignant tumors was far more varied than that observed in patients with benign tumors. The principal reason for this depended largely upon their location within the oral or nasal cavity. Another factor was their more aggressive growth. In eight (42 per cent) of the 19 cases painless swelling was the initial symptom. This is in contrast to the presence of a painless swelling in 85 per cent of the benign tumors. Three patients first noticed painful swelling. Other initial symptoms included local pain without knowledge of the existence of a mass, lacrimation, nosebleed, and nasal discharge. In one patient the presence of tumor was first disclosed when his wife noted a lump in his neck. On investigation this proved to be a metastasis from a tumor primary in the tonsillar region. Other symptoms that occurred during some phase of the disease before medical advice was sought included numbness of one side of the tongue, interference with speech, dryness of the mouth, and sore throat. One patient first noted a painless mass which soon became painful. Lacrimation, trismus, and evidence of weakness of the facial nerve followed in the order given. In the benign tumors pain was by no means a clinical feature, whereas, this symptom was present in most of the malignant tumors before a physician was consulted. The rate of growth in the malignant tumors was described as rapid in about half of the cases. In the remaining cases it was reported as slow and in one was regarded as stationary. In the occasional case one was impressed by a history of recent, rapid enlargement of a tumor which had been quiescent or nearly static for several or many years. None of the patients with benign tumors gave a history of cachexia and weight loss, but this had occurred in three patients with malignant tumors.

Ten of the 19 cases had not been treated prior to examination at Memorial Hospital. In these the duration of symptoms was specifically stated. In six, symptoms had been present for less than one year, usually a short space of months. In four, the duration of symptoms was a year or longer. Included among the latter was a patient with a tumor of the hard palate known to have been present for 25 years. There was a history of rapid enlargement for six weeks during which the overlying mucosa had become ulcerated. On examination a firm cervical lymph node was thought to contain metastatic tumor. Of more than passing interest was the finding that much of the tumor was histologically benign (Fig. 14) but other portions showed the structure of epidermoid carcinoma (Fig. 13). The patient died within a year, after having developed abdominal distress and a large, nodular liver. Another case with similar implications concerned a parotid tumor of six years' known duration with slow enlargement. Growth was described as very rapid for eight months and during this time function of the facial nerve became partially impaired. Radical excision of the parotid salivary gland and tumor combined with radical neck dissection was done. The

primary tumor contained areas that were both benign and malignant in structure and there was metastasis to a single cervical lymph node. These two cases have been briefly presented as evidence of the transformation of benign into malignant tumors.

LOCAL FINDINGS ON FIRST EXAMINATION AT MEMORIAL HOSPITAL

Benign Tumors: The local findings did not differ significantly whether the tumors were or were not recurrent. Those tumors of major salivary glands (20 parotid, one submaxillary) were almost invariably described as firm or moderately firm on palpation. An occasional tumor was regarded as elastic or rubbery. Only two were considered cystic and, hence, this property was much more apparent pathologically than clinically. Whereas, most of the tumors had rather well defined limits on palpation, precise outline was much less common than observed in so-called mixed tumors. As would be expected, the clinical estimation of size in centimeters was greater than that actually found on pathologic examination. The tumors did not center in any particular area of the parotid salivary gland. Five of the 20 benign parotid tumors seemed definitely fixed and several others were not easily movable. One tumor which was recurrent infiltrated skin extensively and caused central ulceration. Another tumor, not recurrent, had also extended into and became fixed to overlying skin, without, however, causing ulceration. Another case presented a recurrent tumor described as fixed and infiltrating skin. Noteworthy, here, was the breakdown of skin and the discharge of large quantities of mucoid material. None of the primary parotid tumors presented any but a single mass but in two recurrent cases there were multiple discrete tumor nodules. No disturbance in the function of the seventh nerve was found except in one case where the nerve had been damaged at a previous operation. The single benign tumor involving the submaxillary salivary gland gave no unique local findings.

The five benign tumors of minor salivary gland origin were submucosal in location with one exception, a polypoid tumor of the nasal cavity. This tumor was also polypoid when it recurred. The other tumors were variously rounded and irregular, firm or moderately firm and more or less fixed. The overlying mucosa was elevated in all cases and in two cases was ulcerated. Neither of these tumors was recurrent. The regional distribution of the benign tumors of minor salivary gland origin is shown in Table II.

Malignant Tumors: Regardless of whether the malignant tumors were primary, recurrent, or of major or minor salivary gland origin, they were with little exception firm, fixed, poorly circumscribed and infiltrative. One of the submaxillary gland tumors was felt to be partly cystic. Both of the submaxillary tumors had fungated through skin. The growth of one parotid tumor interfered with the function of branches of the facial nerve. In this case there had been no previous treatment, the tumor had been slowly enlarging for six years but had exhibited rapid growth for eight months. Mucosal ulceration was present in all but two cases of minor

salivary gland origin. Further local complications caused by intraoral and intranasal tumors were erosion and penetration of adjacent bony structures.

RECURRENCE AND METASTASIS

Patients with Benign Tumors: Eleven of the 26 cases in this group had tumors recurrent after surgery when first seen at Memorial Hospital, and three of these 11 were twice recurrent. The time-interval between excision and the recognition of recurrence varied greatly. Precise dates were recorded in nine cases and were nine years, five years, two years, ten months (two cases), three months, two months (two cases), and one month. Thus, as in other types of salivary gland tumors late recurrence may be a clinical characteristic. Ten of the recurrent tumors were of parotid origin and the other arose in the nasal cavity. The latter tumor had been discovered on routine physical examination and had been excised under the clinical diagnosis of nasal polypus.

Patients with Malignant Tumors: Of 19 such cases nine were recurrent after surgery when first seen at Memorial Hospital. Five of the nine recurrent cases had had more than one reëxcision for recurrent tumor. The time-interval between operation and clinical recurrence was characteristically a short space of months but in a single case there was a lapse of seven years. It is, thus, apparent that rapid recurrence is far more likely in the malignant than the benign muco-epidermoid tumors.

On initial examination ten patients had clinical evidence of metastasis. This was confirmed pathologically in eight. The metastatic lesions involved cervical lymph nodes in all but one instance. In this the supraclavicular nodes contained secondary deposits from a tumor primary in the submaxillary salivary gland. Four of the primary tumors arose in major and six in minor salivary glands of the oral cavity. In six of the ten cases presenting with metastatic lesions there had been no previous treatment.

The material available afforded relatively little opportunity to study the distribution of distant metastases. There were only two autopsies and in one metastases were limited to cervical nodes. In the other there were extensive generalized metastases including regional, mediastinal, para-aortic and iliac lymph nodes, lungs, pleurae, myocardium, liver, and subcutaneous tissue. The primary tumor was located on the alveolar ridge. In another case there was clinical evidence of metastases to the liver. With some surprise it was found that in three cases (including the above mentioned case with autopsy) distant subcutaneous metastases developed. Regions involved included the face, scalp, axilla, and abdomen and in each case positive excisional biopsies were secured (Fig. 4).

RESULTS OF TREATMENT

Benign Tumors: In 14 cases more than five years have elapsed since the beginning of treatment at Memorial Hospital. Three of these were lost to follow-up and were free of disease less than one year, two and two and one-half years when lost. Nine cases were alive and free from disease and

two cases had developed recurrent tumors, one definitely inoperable, the other probably inoperable.

Two of the nine five-year cures were accomplished by irradiation measures alone. One of these cases was that of a parotid tumor recurrent after surgical excision. It measured 5 x 3 cm. in greatest dimensions. The insertion of gold-filtered radon seeds, totalling 25 millicuries destroyed, was followed by complete regression. The other case cured by irradiation alone presented a previously untreated 3-cm. tumor of the mucosa of the cheek situated posteriorly between the upper and lower alveolus. Between June 18 and 26, 1934, the patient received 2000 r of 200 K. V. roentgen ray through a 7-cm. field in single fractions of 250 r, 0.5 mm. copper filtration, target-skin distance 63 cm. One month after the completion of this cycle there was moderate regression and at this time gold seeds, totalling 22.4 millicuries destroyed, were inserted into the tumor. Gradual, complete regression followed.

Of the seven remaining five-year cures, three had surgical excision alone. All of these were parotid tumors, two were previously untreated and one was recurrent two years after surgical excision. None recurred after treatment at Memorial Hospital.

Four of the nine cases cured for five years, or more, received combined surgical and radiation treatment. None of these tumors recurred after treatment. Three of these tumors were of parotid and one of submaxillary salivary gland origin. In each of these four cases gold seeds were implanted at the time of operation in the area from which the tumor had been excised. The amount of radon seed implantation was not uniform, and was recorded as 9, 10, 23.6, and 29.9 millicuries destroyed. One of these four cases received in addition to the interstitial irradiation, 48,000 milligram-hours with the four gram radium element pack in daily fractions of 4,000 milligram-hours. In these cases treated by combined surgery and irradiation it is impossible to evaluate the rôle of irradiation in cure.

There was not sufficient material among the benign tumors to estimate the effect of external irradiation. In only one case was this form of therapy employed in appreciable amount. This was a case of nonrecurrent parotid tumor which was surgically excised and treated postoperatively with 220 K. V. roentgen ray through a 4-cm. cone, in daily fractions of 200 and 300 r, 0.5 mm. copper filtration, target-skin distance 50 cm., for a total of 4900 r. This tumor recurred in less than a year.

Malignant Tumors: The highly fatal character of this group can be shown by briefly enumerating facts concerning those patients known to be dead or alive. Seven are dead. The duration of life after treatment was undertaken at Memorial Hospital was two, three, five, eight, and nine months, two and ten years. The last patient succumbed to both locally recurrent and metastatic tumor as shown by biopsy after having been free from evidence of disease for five years. Five of the seven fatal cases had clinical or pathologic evidence of metastases (usually cervical node) when treatment was begun. Twelve patients are living, but two of these are dying

with locally uncontrolled tumor and a third is known to have subcutaneous metastases. One patient, alone, is alive and free from evidence of tumor for more than five years. Two patients are living three and one-half and two years, respectively, following therapy, and are believed free from disease. The first of these cases was a recurrent parotid tumor without metastases and surgical excision was the only treatment. The second was a primary tonsillar tumor with cervical node metastases treated with external and interstitial irradiation. The follow-up period in the remaining eight cases still living is too short for significant comment.

The purpose in presenting the preceding data on the results of treatment has been to establish the contrasting clinical behavior of the tumors variously classified as benign and malignant. It is inappropriate, and beyond the capabilities of pathologists, to decide on methods of treatment in a class of tumors presenting so many complexities related to specialized regional surgery and the application of various forms of irradiation therapy.

SUMMARY

A little recognized group of salivary gland tumors has been presented and the term, "muco-epidermoid" tumor, applied to them. Reasons have been advanced implicating the salivary gland ducts as their anatomic site of origin. These tumors are believed to represent a specific pathologic type distinct from generally accepted varieties of salivary gland tumors. The 45 tumors included herein have been separated into two groups, benign and malignant, as qualified in the text. Their pathologic aspects have been discussed in full and these have been correlated with clinical behavior.

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